IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IFW $

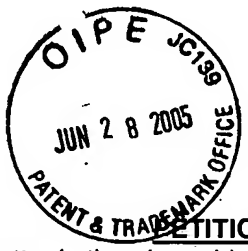
In re Patent Application of Atty Dkt. 620-282
C# M#

TICKLE, et al. TC/A.U. 1652

Serial No. 10/690,991 Examiner: NASHED, Nashaat

Filed: October 23, 2003 Date: June 28, 2005

Title: CRYSTAL STRUCTURE OF CYTOCHROME P450



Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **0** minus highest number previously paid for **20** (at least 20) = 0 x $50.00	$0.00 (1202)/$0.00 (2202)	$	
Independent claims after amendment **0** minus highest number previously paid for **3** (at least 3) = 0 x $200.00	$0.00 (1201)/$0.00 (2201)	$	
If proper multiple dependent claims now added for first time, (ignore improper); add	$360.00 (1051)/$180.00 (2051)	$	
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s)	One Month Extension $120.00 (1251)/$60.00 (2251) Two Month Extensions $450.00 (1252)/$225.00 (2252) Three Month Extensions $1020.00 (1253/$510.00 (2253) Four Month Extensions $1590.00 (1254/$795.00 (2254)	$	
Terminal disclaimer enclosed, add	$130.00 (1814)/ $65.00 (2814)	$	
☐ Applicant claims "small entity" status. ☐ Statement filed herewith			
Rule 56 Information Disclosure Statement Filing Fee	$180.00 (1806)	$	
Assignment Recording Fee	$40.00 (8021)	$	
Other: Petition Fee $130.00 (1460)		$	**130.00**
	TOTAL FEE ENCLOSED	$	**130.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

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NIXON & VANDERHYE P.C.
By Atty: B. J. Sadoff, Reg. No. 36,663

Signature: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

TICKLE, et al.

Serial No. 10/690,991

Filed: October 23, 2003

Atty. Ref.: 620-282

TC/A.U.: 1652

Examiner: NASHED, NASHAAT T

For: CRYSTAL STRUCTURE OF CYTOCHROME P450

* * * * * * * * * * * *

June 28, 2005

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

PETITION TO MAKE SPECIAL

Pursuant to 37 C.F.R. 1.102(d), Applicants hereby petition to make the present application special whereby the application is advanced out of turn for examination.

Pursuant to §708.02 Section VIII of the MPEP (SPECIAL EXAMINING PROCEDURE FOR CERTAIN NEW APPLICATIONS - ACCELERATED EXAMINATION), the present application complies with each of the items identified in that section.

(A) The requisite fee as set forth in 37 C.F.R. 1.17(h) ($130.00) is submitted herewith.

(B) The pending claims presented for examination are directed to a single invention. If it is determined that all of the claims presented are not directed to a single invention, Applicants will make an election without traverse pursuant to any restriction requirement made by the Examiner.

06/29/2005 HLE333 00000061 10690991

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(C) A pre-examination search has been carried out by way of the following three (3) PCT International Search Reports (copies attached):

(i) Partial International Search dated January 9, 2003 in connection with PCT/GB02/01575 (hereinafter referred to as "CP1");

(ii) International Preliminary Examination Report and International Search Report dated August 23, 2004 in connection with PCT/GB02/02668 (hereinafter referred to as "CP2"); and

(iii) International Preliminary Examination Report and International Search Report dated January 27, 2005 in connection with PCT/GB03/04598 (hereinafter referred to as "CP3").

The following claims of these foreign applications, which are of the same or similar scope to the claims in the above-identified U.S. application, were searched in the noted Search Reports:

CP1

Claim 14. A crystal of a cytochrome P450.

Claim 17. The crystal of claim 14 wherein said P450 is 3A4 having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º; or having a space group C2 and unit cell size a=152Å, b=101 Å, c=78Å (+/- 5% for a, b and c), α=90°, β=120°, γ=90°.

CP2

Claim 14. A crystal of a cytochrome P450.

Claim 17. The crystal of claim 14 wherein said P450 is 3A4 having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º; or having a space group C2 and unit cell size a=152Å, b=101 Å, c=78Å (+/- 5% for a, b and c), α=90°, β=120°, γ=90°.

CP3

Claim 61. A crystal of P450 3A4.

Claim 62. The crystal of claim 61 in apo form.

Claim 63. A crystal of P450 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions.

Claim 64. The crystal of any one of claims 61 to 63 wherein said 3A4 comprises the sequence of SEQ ID NO:2

Claim 65. A crystal of P450 3A4 protein having a resolution better than 3.1 Å.

Claim 66. A crystal of P450 protein having the structure defined by the co-ordinates of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å.

One copy of each reference cited in the noted Search Reports has been filed with the Information Disclosure Statements of December 23, 2003, March 5, 2004 or April 13, 2004.

The following is a detailed discussion of the references cited in the Search Reports, which discussion points out, with particularity required by 37 CFR 1.111(b) and (c), how the claimed subject matter is patentable over the references.

1: VON WACHENFELDT C ET AL: "Microsomal P450 2C3 is expressed as a soluble dimer in Escherichia coli following modification of its N-terminus." ARCHIVES OF BIOCHEMISTRY and BIOPHYSICS.UNITED STATES 1 MAR 1997, vol. 339, no. 1, 1 March 1997 (1997-03-01), pages 107-114, XP002222918, ISSN: 0003-9861 (cited in CP1, CP2 and CP3)

VON WACHENFELDT is understood to teach isolation and purification of variants of cytochrome P450 2C3 and 2C5 that lacked a putative membrane segment at the N-terminus. The aim of the disclosure was an attempt to facilitate crystallisation.

VON WACHENFELDT is not understood to teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º. Nor does the document teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as claimed in the above-identified application.

> **2:** COSME J ET AL: "Engineering microsomal cytochrome P450 2C5 to be a soluble, monomeric enzyme. Mutations that alter aggregation, phospholipid dependence of catalysis, and membrane binding." THE JOURNAL OF BIOLOGICAL CHEMISTRY. UNITED STATES 28 JAN 2000, vol. 275, no. 4, 28 January 2000 (2000-01-28), pages 2545-2553, XP002222919, ISSN: 0021-9258 (cited in CP1, CP2 and CP3)

COSME is understood to teach that substitution of residues of cytochrome P450 2C5 with residues derived from cytochrome P450 2C3 produced monomeric and soluble protein. The changes made to the protein are understood to have facilitated crystallisation of the modified cytochrome P450 2C5, 2C5/3LVdH, and allowed determination of the structure by X-ray diffraction studies.

COSME does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

3: WILLIAMS P A ET AL: "Microsomal cytochrome P450 2C5: comparison to microbial P450s and unique features." JOURNAL OF INORGANIC BIOCHEMISTRY, UNITED STATES 31 AUG 2000, vol. 81, no. 3, 31 August 2000 (2000-08-31), pages 183-190, XP002222920, ISSN: 0162-0134 (cited in CP1).

WILLIAMS is understood to teach a crystal structure of a microsomal P450, and specifically P450 2C5 from rabbit. The crystal structure was apparently solved by constructing a chimera of cytochrome P450 2C5, 2C5/3LVdH, which possesses five substitutions derived from cytochrome P450 2C3. The reference is understood to provide a comparison of the structure with that of microbial cytochrome P450s identifying the structural differences that confer specificity of substrate interaction.

WILLIAMS does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor

does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

> **4:** WILLIAMS P A ET AL: "Mammalian microsomal cytochrome P450 monooxygenase: structural adaptations for membrane binding and functional diversity." MOLECULAR CELL. UNITED STATES JAN 2000, vol. 5, no. 1, January 2000 (2000-01), pages 121-131, XP002222921, ISSN: 1097-2765 (cited in CP1, CP2 and CP3)

WILLIAMS is understood to teach a crystal structure of a mammalian microsomal cytochrome P450, and specifically cytochrome P450 2C5 from rabbit. The crystal structure was apparently solved by constructing a chimera of 2C5, 2C5/3LVdH, which possesses five substitutions derived from cytochrome P450 2C3. The crystals belong to the space group I222, with cell dimensions a = 74.7 Å, b = 132.0 Å, and c = 172.4 Å. The atomic co-ordinates of cytochrome P450 2C5/3LVdH were deposited with the Protein Data Bank under entry code 1DT6.

WILLIAMS does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a

crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

5: U.S. Patent No. 5,886,157 A (GILLAM ELIZABETH M J ET AL), 23 March 1999 (1999-03-23) (cited in CP1)

U.S. Patent No. 5,886,157 A is understood to teach a nucleic acid encoding a human cytochrome P450 2E1 comprising a 5' terminal deletion of 63 nucleotides, and a nucleic acid encoding a human cytochrome P450 2C10 containing a 5' terminal deletion of nucleotides 7 through 60. The patent is also understood to provide a method of purifying a recombinant cytochrome P450 protein from membranes from a host cell culture, and purifying recombinant human cytochrome P450 1A1 which has retained catalytic activity.

U.S. Patent No. 5,886,157 A does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

6: HASEMANN C A ET AL: "Crystal Structure and Refinement of Cytochrome P450terp at 2.3 Å Resolution" JOURNAL OF MOLECULAR BIOLOGY, LONDON, GB vol. 236, no. 4, 1994, pages 1169-1185, XP001120740, ISSN: 0022-2836 (cited in CP2 and CP3).

HASEMANN is understood to describe the crystals, structure determination and the crystal structure of a bacterial P450 - cytochrome P450 terp. The crystals have the space group $P6_122$ and cell dimensions a=b=69.4 Å, c=456.6 Å, $\alpha=\beta=90^{\circ}$, $\gamma=120^{\circ}$. The atomic co-ordinates of cytochrome P450 terp were deposited with the Protein Data Bank as entry code 1CPT.

HASEMANN does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), $\beta=90^{\circ}$, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

7: LEWIS DAVID F V: " Homology modelling of human cytochromes P450 involved in xenobiotic metabolism and rationalization of substrate selectivity." EXPERIMENTAL AND TOXICOLOGIC PATHOLOGY, vol. 51, no. 4-5, July 1999 (1999-07), pages 369-374, XP009003755, ISSN: 0940-2993 (cited in CP2 and CP3).

LEWIS is understood to describe the construction of a homology model of cytochrome P450 3A4 and other P450 isoforms based on the crystal structure of bacterial P450 CYP102 (also known as P450 BM-3) as a template. The paper states that P450 3A4 has 27% sequence identity to CYP102 haemoprotein domain. The alignment of amino acid sequences of human P450s with bacterial P450 CYP102 is generated and used to create a model of 3A4 by homology with the bacterial P450.

LEWIS does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

8: IBEANU G C ET AL: "Identification of residues 99, 220, and 221 of human cytochrome P450 2C19 determinants of omeprazole hydroxylase activity" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 271, no. 21, 24 May 1996 (1996-05-24), pages 12496-12501, XP001017944, ISSN: 0021-9258 (cited in CP2).

IBEANU is understood to teach that amino acids 99, 220 and 221 are key residues in cytochrome P450 2C19 that determine the specificity of P450 2C19 for omeprazole. To identify the critical amino acids that determine the specificity of human

P450 2C19, the authors describe the construction of several chimeras where residues and substrate binding sites of P450 2C9 are replaced with those of P450 2C19.

IBEANU does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

9: SUEYOSHI TATSUYA ET AL: "Molecular engineering if microsomal P450 2a-4 to a stable, water-soluble enzyme" ARCHIVES OF BIOCHEMISTRY AND BIOPHYSICS vol. 332, no. 1, 1995, pages 265-271, XP002268607, ISSN: 0003-9861 (cited in CP3)

SUEYOSHI is understood to describe the replacement of the NH_2-terminal hydrophobic anchor domain of 2a-4 with an amphipathic peptide such as peptitergent to provide method for engineering membrane-bound P450s to soluble enzymes. The genetically engineered peptitergented P450 2a-4 was expressed in *Escherichia coli* and purified without the use of detergents to produce a water-soluble form of mouse microsomal 2a-4.

SUEYOSHI does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit

cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

10: DE 195 49 267 A (MAX DELBRUECK CENTRUM), 3 July 1997 (1997-07-03) (cited in CP3).

DE 195 49 267 A is understood to disclose a method to crystallize proteins by inducing crystal formation in protein solutions using ultracentrifugation to induce nucleation. A highly saturated protein solution is centrifuged, the protein concentration distribution in the centrifuge tube is analyzed, and the centrifugation stopped when crystal nuclei of a predetermined size and concentration are present. The patent application discloses that centrifugation induces formation of stable associates that will form crystals. The process is stated as being capable of being used for crystallising fibrinolytic proteins, especially plasminogen, plasminogen activators, streptokinase and staphylokinase, and membrane proteins, especially cytochrome P450, e.g. for X-ray crystallography. The examples involve the crystallization of lysozyme and papain using ultracentrifugation. DE 195 49 267 A does not disclose any crystals of cytochome P450.

DE 195 49 267 A does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

11: WO 99/08812 A (UNIV ROCHESTER), 25 February 1999 (1999-02-25) (cited in CP3).

WO 99/08812 A is understood to disclose DNA encoding chimeric bacterial and mammalian P450 proteins. The chimeric DNA encodes fusion proteins which are soluble, active and useful in bioremediation of pollutants. Since the protein is soluble it is stated that it could prove a method for obtaining structural information in particular it will lend itself to structural elucidation by X-ray crystallography. The patent application discloses chimeras of P450 cytochrome 2C9 and P450cam.

WO 99/08812 A does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains

the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

> **12:** EKINS S ET AL: "Pharmacophore and Three-Dimensional Quantitative Structure Activity Relationship methods for Modeling Cytochrome P450 Active Sites" DRUG METABOLISM AND DISPOSITION vol. 18, no. 7, July 2001 (2001-07), pages 936-944, XP001122105, ISSN: 0090-9556 (cited in CP3).

EKINS is understood to describe how, in the absence of crystal structures of human cytochrome P450s, computer approaches like structure activity relationships (SAR), three-dimensional quantitative structure activity relationships (3D-QSAR), and pharmacophores are used to understand cytochrome P450 active sites and cytochrome P450 induction. The paper reviews existing pharmacophores and 3D-QSAR models of human cytochrome P450s including cytochrome P450 3A4, which can be used to classify molecules for their likely ability to be cytochrome P450 substrates or inhibitors.

EKINS does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 ± a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

13: U.S. Patent No. 6,312,917 B1 (CHEN CUIPING ET AL) 6 November 2001 (2001-11-06) (cited in CP3).

U.S. Patent No. 6,312,917 B1 is understood to teach a method of screening a candidate compound for susceptibility to metabolism by a selected enzyme, wherein a preferred example of the selected enzyme is a cytochrome P450. The method includes the steps of reacting the candidate compound, an indicator compound precursor and the selected enzyme, the selected enzyme being characterized as having a side reaction associated with metabolic activity of the enzyme wherein a chemical species capable of reacting with the indicator compound precursor is produced. The indicator compound produced from reaction of the indicator compound precursor with the chemical species produced from the side reaction is then detected, indicating the susceptibility of the candidate compound to metabolism by the enzyme. The examples describe an application of this using 3A4 and 1A2 with a fluorescent indicator compound.

U.S. Patent No. 6,312,917 B1 does not teach or suggest crystals of 3A4 having an orthorhomobic space group I222, and unit cell dimensions 78 Å, 100 Å, 132 Å, 90°, 90°, 90°, with a unit cell variability of 5% in all dimensions or having a space group I222 and unit cell size a=77 Å, b=99 Å, c=129 Å, (+/- 5% for a, b and c), β=90º, as presently claimed. Nor does the reference teach or suggest crystals wherein the 3A4 contains the sequence of SEQ ID NO:2, as presently claimed. Further the reference does not teach or suggest a crystal of P450 3A4 protein having the structure defined by the co-ordinates of Table 5 $\pm$ a root mean square deviation from the Cα atoms of not more than 1.5 Å, as presently claimed.

Further art was filed with the Information Disclosure Statements filed March 5, 2004, July 20, 2004 and October 1, 2004. The requirements of MPEP § 708.02 (VIII)(E) are understood to apply to the documents cited in the Search Reports however the Examiner is requested to contact the undersigned in the event anything further is required in this regard.

The Examiner is requested to initial the previously-submitted PTO-1449 Forms and to return copies of the initialed documents to the undersigned as an indication that the previously-filed references have been considered and made of record.

(D) As noted above, copies of all of the cited art were previously submitted.

(E) A detailed discussion of the references cited in the Search Reports, which points out with the particularity required by 37 CFR § 1.111(b) and (c), how the claimed subject matter is patentable over the references, is provided above.

Expedited action on the present application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

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Attachments:
Copies of PCT International Search Reports

(Partial International Search dated January 9, 2003 in connection with PCT/GB02/01575;
International Preliminary Examination Report and International Search Report dated August 23, 2004 in connection with PCT/GB02/02668; and
International Preliminary Examination Report and International Search Report dated January 27, 2005 in connection with PCT/GB03/04598)

Rule 17(h) Petition Fee ($130.00 – fee code 1464)